REMARKS

1. Preliminary Remarks

a. Status of Claims

Claims 21, 44, and 50-53 are pending in this application. Claims 21 and 51 are amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of these amendments, claims 26, 31, 33, and 35-37 will be pending and under active consideration.

b. Amendment to the Claims

In order to expedite prosecution and without prejudice to seeking claims directed to similar subject matter, claims 21 and claims 51 have been amended to be directed to an isolated nucleic acid wherein the sequence of the nucleic acid consists of (a) SEQ ID NO: 4642 or 1917, (b) an RNA equivalent of (a), or the complement of (a) or (b), wherein the complement is identical in length to the nucleic acid of (a) or (b). No new subject matter has been introduced by these amendments.

c. Objection the Specification

On page 2 of the Office Action, the Examiner objects to the summary of the invention by asserting that Applicant is allegedly required to modify the brief summary of the invention and restrict the descriptive manner to be in harmony with the claims. The Examiner points to MPEP §1302.01 for support of the objection. Applicant respectfully disagrees.

The Examiner's reference to §1302.01 MPEP is misguided as this section is directed by the U.S. Patent Rule 37 C.F.R. §1.73, which does not absolutely require that the summary of invention be in complete harmony with the claims. Specifically, §1302.01 of the MPEP states "patents **should** be confined in their disclosure to the respective inventions patented" and points to 37 C.F.R.§1.73 states that the "summary **should**, when set forth, be commensurate with the invention as claimed and any object recited should be that of the invention as claimed." Nowhere in 37 C.F.R. §1.73 is there an absolute requirement to restrict the brief summary of the invention to be in harmony with the claims. Applicant submits that the description in the summary of the invention sufficiently covers the scope of the claimed invention and therefore request that the Examiner withdrawn the objection.

d. Non-Statutory Obviousness-Type Double Patenting

On pages 2-4 of the Office Action, the Examiner provisionally rejects claims 21, 44, and 50-53 on grounds of nonstatutory obviousness-type double patenting.

(1) Over U.S. Patent Appl. No. 10/605,838

The Examiner maintains that the instant claims are unpatentable over claims 1-3, 8, 11, and 12 of copending U.S. App. No. 10/605,838 (the "'838 Application"). The instant application was filed on

August 29, 2003, which predates the filing date of October 30, 2003 for the '838 Application. Because the instant application was filed earlier, Applicant respectfully requests that the obviousness-type double patenting rejection over the '838 Application be withdrawn pursuant to M.P.E.P. § 804.I.B1.

(2) Over U.S. Patent Appl. No. 10/536,560

The Examiner asserts that claims 21, 44, and 50-53 of the instant application are unpatentable over claims 21, 27, 33, 34, 35, 41, 47, and 478 of co-pending U.S. Patent Appl. No. 10/536,560 (hereafter the "'560 Application"). The instant application was filed on August 29, 2003, which predates the filing date of November 26, 2003 for the '560 Application. Because the instant application was filed earlier, Applicant respectfully requests that the obviousness-type double patenting rejection over the '560 Application be withdrawn pursuant to M.P.E.P. § 804.I.B1.

2. Patentability Remarks

a. 35 U.S.C. §101

On pages 4-10 of the Office Action, the Examiner rejects claims 21, 44, and 50-53 under 35 U.S.C. §101 for lacking support in the specification for credible utility. The Applicant respectfully disagrees.

Specifically, the Applicant asserts that the Examiner has impermissibly applied a higher evidentiary standard for establishing utility of the claimed nucleic acids. The evidentiary standard that the Patent Office **should** use throughout *ex parte* examination in setting forth the utility rejection is preponderance of the totality of the evidence under consideration. A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is true. *See Herman v. Huddleston*, 459 U.S. 375 (1983). To overcome the presumption of truth of the Applicant's assertion of utility, the Examiner must establish by presenting countervailing facts that it is more likely than not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility.

The crux of the Examiner's rejection is that the Applicant's assertion that the claimed miR nucleic acids do bind and inhibit expression of COL6A1 mRNA lacks credibility. The Examiner asserts that the prediction model taught by the Applicant provides no evidence that the claimed nucleic acids function as miRNA-like molecules. The Examiner presents the alleged countervailing facts that at the time of filing, prediction of miRNAs yielded predictions that were not valid citing John *et al.*, *PloS Biology* 2:1862-1879 (2004)(hereafter "John"), and points to page 1865 in John that states that the "percentage of false positives for target transcripts with more than two, three, and four sites is 39%, 30%, and 24% respectively" and "false positive rates for single sites is about 35%". Moreover, the Examiner repeatedly states that the function of SEQ ID NO: 4642 as a functional miRNA that targets and modulates expression of COL6A1 must be shown experimentally and states that the experimental evidence that the

claimed Epstein Barr Virus related nucleic acids regulate the asserted target COL6A1 is argumentative and requires a declaration.

A careful review of the basis of the rejection shows that the Examiner requires experimental certainty or 100% assurance that the claimed nucleic acids act or form a miRNA in order to remove any question of truth to the stated utility. Applicant submits this application of the law is impermissible.

Applicant submits that an assertion is credible unless (A) the logic underlying the assumption is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. For example, as discussed in §2107.02 III B of the MPEP, an assertion of utility would not be considered credible where a person of ordinary skill would consider the assertion to be "incredible in view of contemporary knowledge" and where nothing offered by the Applicant would counter what contemporary knowledge might otherwise suggest. Rejections under 35 U.S.C. §101 based on lack of credible utility have been sustained by federal courts when the applicant failed to disclose **any** utility for the invention or asserted a utility that could only be true if it **violated a scientific principle or was wholly inconsistent with contemporary knowledge in the art.** *See In re Gazave*, 379 F.2d 973 (CCPA 1967).

In response to the Examiner's assertions and the stated law above, the Applicant first asserts that the Examiner has provided no evidence to countervail that miRNA SEQ ID NO: 4642 is likely to inhibit expression of the COL6A1 protein. Whether or not the claimed polynucleotides actually exist in a biological system, and whether the true biological function of any predicted miRNA sequence has been validated according to Krutzfeldt (cited again by Examiner on page 6 of the Office Action) are irrelevant. The proper inquiry is instead whether a person of ordinary skill in the art would believe that the claimed polynucleotides **may be** used to modulate expression of the specific mRNA targets. Applicant submits evidence has been presented throughout the file history of this application.

For example, paragraph [0120] of the application discloses that the mRNA targets of the claimed polynucleotides were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described in paragraph [0003], [0005], [0172], and [0186] for identifying target binding sites of miRs is based upon studies at the time of filing demonstrating that miRs bind to target binding sites as disclosed in references such as Wightman *et al.* (1993), Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all cited in the Information Disclosure Statement filed herewith. Accordingly, Applicant's algorithm does not violate any scientific principle and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms and the Examiner's cited algorithm from John, which itself predict miRNA/target biding at a 69-78% success rate. The Applicant further submits that the Examiner has failed to present the required countervailing facts that it is more likely than

not that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. In other words, the Examiner has failed to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility. Accordingly, the Examiner has failed to provide by a preponderance of the evidence that Applicant's asserted utility fails.

Nevertheless, the Applicant submits herewith experimental evidence in the form of a declaration by Dr. Ayelet Chajut under 37 C.F.R. §1.132 (the " Declaration"), which validates that the claimed nucleic acids regulate the asserted target COL6A1. The Declaration provides methods and results of experiments that Dr. Chajut supervised and conducted in order to test that the claimed Epstein-Barr Virus-related nucleic acids regulate the asserted target COL6A1. Quantitative reverse transcription PCR was used to compare the level of COL6A1 mRNA in peripheral blood mononuclear cells (PBMC), which do not normally express EBV-miR-BART1-3P (SEQ ID NO: 4642), to the level in PBMC that have been infected with EBV (See paragraph 5 of the Declaration). In paragraph 6 of the Declaration, Dr. Chajut states that uninfected PBMC has a 50-Ct value of over 22 for COL6A1 mRNA, while EBV-infected PBMC had 50-Ct of less than 16. Thus, the level of COL6A1 mRNA in Epstein Barr virus infected PBMC cells is significantly decreased approximately 120-fold (i.e., $2^{(50-Ct}=2^{(22.9-16)}$) compared to uninfected cells (See paragraph 6 of the Declaration). Applicant submits that this is evidence that the claimed nucleic acids (ebv-miR-BART1-3P; SEQ ID NO: 4642) are expressed by EBV and regulate the asserted target COL6A1 mRNA.

Applicant submits that unlike the facts in *Gazave*, Dr. Chajut's Declaration validates that Applicant's algorithm does not violate any scientific principles and is wholly consistent with contemporary knowledge regarding miRNA prediction algorithms. In summary, credibly utility of the claimed nucleic acids exists after consideration of the teachings of the specification in combination with Examiner's failure to provide greater than 50% assurance that one of ordinary skill in the art would doubt (or question) the truth of the statement of utility as well as the Applicant's unnecessary step of providing the Examiner with validation results described in the Declaration. Accordingly, the Examiner has failed to provide by a preponderance of the evidence that Applicant's asserted utility fails.

With regard to the Examiner's rejection regarding specific and substantial utility, the Examiner has not provided any further comment than those made in the previous office action dated February 11, 2008. Applicant reasserts that the claimed nucleic acids are of a specific and unique nature because these nucleic acids regulate the translation of mRNAs from the specific target gene COL6A1. Applicant also presents again the fact that study of the regulation of COL6A1 is a public benefit one reason which is the ability of the claimed nucleic acids to modulate the expression of the COL6A1 in order to alter collagen VI assembly and secretion.

Accordingly, Applicant asserts that the claimed nucleic acids have specific, substantial and credible utility. In view of the foregoing, Applicant requests that the rejection of claims 21, 44, and 50-53 under 35 U.S.C. §101 for lacking utility has been overcome and therefore should be withdrawn.

b. 35 U.S.C. §112, First Paragraph (Enablement)

On page 8 of the Office Action, the Examiner maintained the rejection of claims 21, 44, and 50-53 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. The Examiner asserts that since the claimed invention is not supported by a credible asserted utility, one skilled in the art would not know how to use the claimed invention. Applicant respectfully disagrees.

As discussed above, the claimed nucleic acids have a credible, substantial and specific utility, namely in modulating expression of the COL6A1 transcript, which in turn, may respectfully alter collagen VI assembly and secretion.. Therefore, the Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing remarks Applicant respectfully requests that the rejection of claims 21, 44, and 50-53 under 35 U.S.C. §112 for lack of enablement has been overcome and therefore should be withdrawn.

Respectfully submitted,

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